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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/127,364	07/31/1998	THEODORE A. YEDNOCK	193-US-CIP2	1040

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EXAMINER
LUKTON, DAVID

ART UNIT	PAPER NUMBER
1653	20

DATE MAILED: 07/09/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/127,364	Yednock
Examiner	**Art Unit**
David Lukton	1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 11, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *24-36* is/are pending in the application.

4a) Of the above, claim(s) *24-30* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *31-36* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Applicants' election of Group 5 with traverse (claims 31-36, limited to G3) is acknowledgd. Also acknowledged are the "species" [(a) a specific *alpha*-9 antagonist compound that is administered to the subject, and (b) asthma as the specific "inflammatory condition"].

Pursuant to the directives of paper No. 19 (filed 4/11/02), claims 1-10 have been cancelled, and claim 24 amended.

Applicants have made arguments with respect to the non-elected claims. However, these arguments are rendered moot by the election of claims drawn to treatment of inflammation. Applicants have also argued that G3 and G4 should be rejoined. While there is some merit to applicants' arguments with respect to this particular issue, rejoining of Groups 5 and 6 is not undertaken at the present time. However, in the event that both of the following conditions are met, rejoining of subgenera G3 and G4 is likely: (a) subgenus G4 proves to be novel in its present form and (b) applicants do not "extract out" genera of compounds from other applications and insert them into one of the pending claims.

In this Office action, claims 31-36 are examined in part.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As stated on page 32, line 3+, each of the compounds of examples 1-373 of application 08/904424 exhibited an IC_{50} of 15 micromolar or less in an assay which measures antagonism of the compounds to VLA-4. It does not appear that applicants have tested the compounds in an assay of alpha-9 integrin antagonism; however, if applicants are asserting that there exists a correlation between the propensity of a compound to antagonize VLA-4, and the propensity of the compound to antagonize alpha-9 integrin, such an assertion will be left unchallenged at the present time. However, to the extent that such overlap exists, a finding of "unpredictability" in VLA-4 antagonism will extend to alpha-9 antagonism as well. As stated in the specification (p. 22, line 30+): "*alpha*-9 integrin inhibitor compounds will find particular utility in the treatment of a variety of disorders which include an inflammatory component, particularly those in which the inflammatory component is associated with VLA-4 binding to *alpha*-9 integrin". Also, the sentence bridging pages 13-14 conveys the view that there is overlap between the ligands recognized by the two integrins.

The assertion by the examiner is that (a) structure/activity relationships in VLA-4

antagonism are unpredictable, and (b) treatment of inflammatory conditions is unpredictable as well. Consider the following:

- Dutta (*Journal of Peptide Science* **6**, 321-341, 2000) has examined the efficacy of various peptides in the antagonism of VLA-4/VCAM-1 binding. As stated on page 329, col 2, last two lines, the following two compounds were inactive both *in vitro* and *in vivo*:

  cyclo[Ile-Leu-Asp-Val-NH $(CH2)_2CO$]
  Ac-cyclo(Orn-Leu-Asp-Val)

  These peptides are minor variations of peptides that were active.

- Arrhenius (*USP 5,688,913*) discloses (cols 17-18) several examples of compounds which failed to antagonize VLA-4. These compounds are minor variations of other compounds that were potent antagonists of VLA-4.

- Komoriya, Akira (*J. Biol. Chem.* **266** (23), 15075-15079, 1991) discloses that in an assay of $\alpha_4\beta_1$ activity, the pentapeptide EILEV was active, but pentapeptide EILDV was not. This latter peptide differs from the former by just one methylene unit.

- Haworth, Duncan (*Br. J. Pharmacol.* **126**(8), 1751-1760, 1999) discloses various VLA-4 antagonists. At least one of the disclosed compounds was inactive; this compound differed by only a few methylene units from a compound that was active.

- Haubner (*J. Am. Chem. Soc.* **118**, 7881, 1996) discloses (table 2) two compounds which failed to inhibit fibrinogen binding to the $\alpha_{IIb}\beta_1$ receptor, and vitronectin binding to the the $\alpha_V\beta_3$ receptor. The reference also discloses (p. 7882, col 2) that replacement of glycine with alanine in RGD results in a "drastic loss" of activity. These data argue for "unpredictability" in structure activity relationships of integrins generally. In addition, the "unpredictability" in structure activity relationships of RGD-peptides has direct relevance to the claimed compounds. As disclosed in Yang Y (*European Journal of Immunology* **28** (3) 995-1004, 1998) RGD-containing peptides can bind to VLA-4. Thus, if one cannot predict structure activity relationships of RGD peptides in their binding to VLA-4, it stands to reason that such unpredictability extends to other compounds which either do bind VLA-4, or which are asserted to exhibit such an effect.

- In addition to the foregoing, the following references teach "failure" in the treatment of one or more inflammatory conditions:

  Vatistas N J, "Infection of the intertubercular bursa in horses: four cases (1978-1991)", [*Journal of the American Veterinary Medical Association* **208** (9) 1434-7, 1996];

  Tait A, "Synthesis and antiinflammatory activity of 2,6-bis(1,1- dimethylethyl) phenol derivatives" (*Farmaco* **48** (10) 1463-73, 1993);

  Kurokawa M "Synthesis and antiinflammatory activity of cis- and trans- 6,6a, 7,8,9,10,10a,11- octahydro-11-oxodibenzo[b,e]thiepinacetic and -oxepinacetic acids" (*Journal of Medicinal Chemistry* **33** (2) 504-9, 1990);

  Uren M F, "The effect of anti-inflammatory agents on the clinical expression of bovine ephemeral fever" (*Veterinary Microbiology* **19** (2) 99-111, 1989;

  Crossley M J, "Studies on the effects of pharmacological agents on antigen-induced arthritis in BALB/c mice" (*Drugs Under Experimental and Clinical Research* **13** (5) 273-7, 1987).

Thus, structure/activity relationships involving VLA-4 are unpredictable. Perhaps it is true that many of the compounds falling within the scope of claim 35 will exhibit an IC_{50} of 15 *micro*molar in an assay of VLA-4. However, the significance of this number (15 μM) with respect to treatment of treatment of Alzheimer's disease, AIDS dementia, diabetes, atherosclerosis, multiple sclerosis, inflammatory bowel disease, stroke, nephritis, asthma, retinitis, atopic dermatitis, psoriasis, and myocardial ischemia is unknown. No correlation has been established between this "15 μM" parameter, and successful treatment of any of the foregoing diseases. Moreover, other issues such as bioavailability and pharmacokinetics

are not reflected in this "15 μM" number.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988), the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

Nevertheless, an argument can be made that a claim drawn to a method of antagonizing alpha-9 would be enabled. In addition, it may be the case that claims drawn to inhibition of various "downstream" biochemical processes would be enabled as well. The possibility exists that one or more of the following would be enabled:

- A method of inhibiting adhesion of leukocytes to endothelial cells...
- A method of inhibiting bronchoconstriction in a mammal that has been challenged with an allergen...
- A method of inhibiting the release of certain (specific) chemical mediators from leukocytes...
- A method of mitigating damage to tissue that results from release of toxic chemical mediators from leukocytes...
- A method of inhibiting metastasis in a mammal...

As the claims currently stand, however, "undue experimentation" would be required to practice the claimed invention.

*

Claims 31-36 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claims 31-36 are indefinite as to the intended inflammatory conditions.
- Claim 31 recites the phrase "pharmaceutically effective", thus rendering the claims indefinite as to the objectives of the pharmaceutically efficacy.
- The claims are indefinite as to the process steps and endpoint. It is suggested that claim 31 be amended to recite that the compound is administered *for a time and under conditions effective to antagonize alpha-9 integrin.*
- Claim 32 recites that there is increased neutrophil adhesion. To what are the neutrophils adhering?
- In claim 36, line 3, the following is recited: "4-methylpiperzin-1-". However, it appears that the intended spelling is instead the following: 4-methylpiperazin-1- .

*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton. Phone: (703) 308-3213.

An inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

DAVID LUKTON
PATENT EXAMINER
GROUP 1800